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Preoperative anti-inflammatory treatment of diabetic patients does not improve recovery from cataract surgery when postoperatively treated with a combination of prednisolone acetate and nepafenac

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ABSTRACT.

Purpose: **To examine preoperative anti-inflammatory treatment on recovery from cataract surgery in eyes of diabetic patients.**

Methods: **A Prospective randomized clinical trial. One hundred and three eyes of 103 patients with diabetes undergoing routine cataract surgery were randomized (1:1) not to receive any preoperative anti-inflammatory medication or to receive preoperative topical anti-inflammatory medication with a combination of prednisolone acetate (10 mg/ml) and nepafenac (1 mg/ml). All eyes received postoperative anti-inflammatory combination therapy for 3 weeks. Recovery from surgery was recorded by a structured home questionnaire. Clinical outcome parameters were recorded at 28 days and 3 months.**

Results: **Patient age and gender distribution, and all baseline ophthalmic and systemic parameters were comparable between the study groups. After surgery, conjunctival injection lasted 2.4 ± 1.7 days (mean ± SD) and irritation of the eye 3.3 ± 3.9 days in eyes without preoperative treatment, when compared to 1.6 ± 1.6 days (p = 0.067) and 2.4 ± 4.0 days (p = 0.431), respectively, in eyes with preoperative treatment. At 28 days, central subfield macular thickness (CSMT) increased 2.2 ± 20.2 μm in eyes without preoperative treatment, when compared 0.1 ± 25.2 μm (p = 0.670) in eyes with preoperative treatment. At 3 months, the respective CSMT change from baseline was −1.5 ± 26.9 μm and −3.4 ± 26.2 μm (p = 0.762). None of the eyes were reported with pseudophakic cystoid macular oedema (PCME) in either group.**

Conclusion: **Lack of preoperative anti-inflammatory treatment does not impair recovery from surgery or predispose diabetic patients to increased risk of PCME in eyes postoperatively treated with combination therapy of prednisolone acetate and nepafenac.**

Key words: cataract surgery – diabetes – nonsteroidal anti-inflammatory drug – preoperative treatment – pseudophakic cystoid macular oedema – steroid

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Introduction

Cataract surgery with modern techniques is considered a cost-effective and safe healthcare intervention. Pseudophakic cystoid macular oedema (PCME) is among the most common complications of cataract surgery, even in the absence of intraoperative complications or other risk factors (Kessel et al. 2014; Chu et al. 2016; Grzybowski et al. 2016). Postoperative sterile inflammation predisposes eyes to breakdown of the blood–retinal barrier (BRB), increases vascular permeability and the risk for PCME (Ersoy et al. 2013). Patients with diabetes are at recognized risk for PCME (Chu et al. 2016). Particularly, coexistence of diabetic retinal manifestations, insulin dependence and poor glycemic control has been linked with the risk for macular oedema after surgery (Ylinen et al. 2017).

The effectiveness, productivity and safety of health care can be improved by systematically withdrawing outdated practices that are not based on evidence, are not sufficiently effective or may even be harmful. Such methods may have unfavourable balance of anticipated benefits and risks, they may cause unnecessary costs, and are

inferior to other available treatment options. At the present, ophthalmic check-ups after routine cataract surgery may become unnecessary (Eloranta & Falck 2017; Westborg & Monestam 2017). Moreover, use of topical antibiotics pre- and postoperatively is being abandoned since it gives no additional benefit over perioperative intracameral antibiotic administration (Lundstrom et al. 2007, ESCRS Endophthalmitis Study Group, 2007, Friling et al. 2013; Kessel et al. 2017). The development of streamlined clinical eye care processes has resulted in substantial reduction in lead times without compromising patient satisfaction (Lindholm et al. 2018). Similarly, standardization of high-volume eye health services has led to discarding preoperative ophthalmic check-ups for the majority of outpatients requiring cataract surgery. Nevertheless, achieving optimal outcomes and preventing late complications in high-risk patients requires diligent care which also necessitates adequate medical treatment. Diabetic patients for instance, with a risk to develop PCME, are encouraged to be systematically followed by ophthalmologists. In clinical practice for high-risk patients regarding PCME, pre- and postoperative medical interventions with a combination of topical anti-inflammatory drugs are employed to minimize postoperative inflammation (Donnenfeld et al. 2006; Yavas et al. 2007; Kim et al. 2010; Wielders et al. 2015).

The purpose of this study was to assess whether preoperative anti-inflammatory medication has any additional benefit in recovery from surgery, intraocular inflammation and macular oedema after surgery, when the anti-inflammatory treatment after uneventful cataract removal was a combination of potent steroid and nonsteroidal anti-inflammatory drug (NSAID). These results may supplement to our knowledge in planning the optimal schedule and anti-inflammatory treatment protocol for patients with diabetes.

Materials and Methods

Study design

The study was a prospective randomized clinical trial. One hundred and three eyes of 103 patients with diabetes were admitted as per the national guidelines for the management of cataract in the Department of Ophthalmology, Kymenlaakso Central Hospital, Kotka, Finland. Patients were enrolled between March 2017 and March 2018.

Patients were randomized in two groups: those not receiving any preoperative anti-inflammatory medication (later in text referred as PRE−) and those receiving prednisolone acetate (Pred Forte®, 10 mg/ml, Allergan, Inc. Irvine, CA) and nepafenac (Nevanac®, 1 mg/ml, Novartis, Basel, Switzerland) combination therapy three times a day (t.i.d) for 3 days before surgery (later in text referred as PRE+). All patients received a combination of prednisolone acetate and nepafenac t.i.d for 3 weeks as postoperative anti-inflammatory medication. Clinical outcome parameters were recorded at 28 days and 3 months.

The study was conducted according to the tenets of the Declaration of Helsinki and was approved by the Research Director and Chief Medical Officer of the Kymenlaakso Central Hospital, the Finnish Medicines Agency Fimea and the Institutional Review Board of Helsinki University Hospital (EU Clinical Trials Register Number: 2016-004514-10).

Randomization

The study was conducted as a randomized, prospective single-centre study (hrrg.fi/en/clinicaltrials/cataract/). Patients were randomized by a research technician into two groups for the different anti-inflammatory medication protocols described above.

Inclusion criteria

The study subjects were of 60–90 years of age and were eligible for cataract surgery under the Current Care Guidelines of Cataract Surgery of the Finnish Medical Society, Duodecim (updated in 2013).

Exclusion criteria

Exclusion criteria for the study included prior or active wet age-related macular degeneration, retinal vein/artery occlusion, retinal detachment or optic neuritis, previous intraocular procedures (excluding fundus laser photocoagulation), prior or scheduled anti-vascular endothelial growth factor (anti-VEGF) treatment and myopia above −6.0 dioptres. Alcohol abuse, thyroid disease with abnormal thyroid-stimulating hormone (TSH) levels, continuous use of anti-inflammatory drugs and sensitivity to any of the medications used during or after the operation. Criteria for exclusion were also intraoperative complications (such as iris prolapse, use of sutures or posterior capsule tear) or failure to use the anti-inflammatory medication as prescribed.

Patients

Prior to the 28-day control visit four patients were withdrawn at their own request or failure to attend the predetermined control visit (one patient in the PRE− and three patients in the PRE+ study group) (Table 1). Between the 28-day and 3-month postoperative visits, five patients were withdrawn at their own request or failure to attend the predetermined control visit (four patients in the PRE− and one patient in the PRE+ study group) (Table 1).

After these dropouts, a total of 99 eyes were included in the analysis at the 28-day postoperative visit and 94 eyes at the 3-month postoperative visit (Table 1).

Surgery

Prior to the surgery, all eyes were prepared with the combination of tropicamide (Oftan Tropicamid®, 5 mg/ml), phenylephrine hydrochloride (Oftan Metaoksedrin®, 100 mg/ml), levofloxacin (Oftaquix®, 5 mg/ml) and oxybuprocaine hydrochloride (Oftan

Table 1. Flow chart.

Intention-to-treat Randomization	N = 103 eyes	
	PRE−	PRE+
At baseline	N = 52 eyes	N = 51 eyes
At 28 days	N = 51 eyes	N = 48 eyes
At 3 months	N = 47 eyes	N = 47 eyes

Obucain®, 4 mg/ml), all from Santen Pharmaceutical Co. Ltd, Osaka, Japan.

A standardized phacoemulsification technique was used in all cataract surgeries (hrrg.fi/en/videos/cataract/). A 2.75 mm clear cornea incision was followed by capsulorrhexis, phacoemulsification (divide and conquer) and intraocular lens placement into the capsular bag. An Ozil phacoemulsification handpiece and a 0.9 mm 30-degree beveled Kelman tip were used in the phacoemulsification system (Infiniti®, Alcon, Fort Worth, TX). In all cases, anaesthesia was topical. Hyaluronic acid 1.6%-chondroitin sulphate 4.0% (DisCoVisc®, Alcon) was used as ophthalmic viscosurgical device. Preloaded aspheric hydrophobic single-piece monofocal intraocular lenses (PCB00, Tecnis® IOL in iTec® delivery system, Abbott Medical Optics Inc./Johnson & Johnson Vision, Santa Ana, CA; and AU00T0, AcrySof® IQ, SN60WF in UltraSert™ delivery system, Alcon) were used.

In addition to the preoperative use of mydriatics at preparation for the surgery, intracameral phenylephrine was applied in all operations after the clear cornea incision. Antimicrobial medication included intraoperative intracameral cefuroxime (Aprokam®, Laboratoires Thea, Clermont-Ferrand, France). No postoperative antimicrobial medication was used. Cataract surgeries were performed by four specialists and two experienced residents in ophthalmology.

Structured home questionnaire

On the day of surgery, all patients received a structured take-home questionnaire. These home questionnaires were crosschecked by the patient and a research technician at the 28-day postoperative visit, before collecting the data. The regularity of eye drop use, date of conjunctival injection and eye irritation cessation, time to reach maximal and stable visual acuity and overall satisfaction were recorded. Moreover, self-monitored fasting and postprandial blood glucose levels were recorded for 28 days after surgery.

Clinical evaluation

The operating physician examined the patients preoperatively. DR was graded on a four-stage severity classification as none, background, moderate to severe nonproliferative or proliferative DR. Furthermore, all diabetic patients belonged to regular screening system for diabetic retinopathy according to the Current Care Guideline for Diabetic retinopathy of the Finnish Medical Society, Duodecim (updated in 2015).

Preoperative measurements before initiation of anti-inflammatory medication were performed by a trained research technician whom the patients also visited at 28 days and 3 months.

An auto-refractometer (ARK-1s, NIDEK Co. Ltd, Aichi, Japan) was used to evaluate postoperative visual acuity. Intraocular pressure was measured by rebound tonometry (iCare® tonometer, Revenio Group, Vantaa, Finland).

Aqueous flare was recorded by a laser flare metre (FM-600, Kowa Company, Ltd., Nagoya, Japan). The mean of five reliable aqueous flare measurements was used in the analysis. Macular thickness was reported according to the ETDRS retinal thickness map. Central subfield macular thickness (CSMT; defined as the mean thickness in the central 1000-μm diameter area), parafoveal and perifoveal thickness (defined as the mean thickness in a concentric ring 1.0–3.0 mm and 3.0–6.0 mm around the fovea) and total macular volume (TMV; calculated for the central 6.0 mm area) were recorded by a spectral-domain optical coherence tomography (SD-OCT; Heidelberg Eye Explorer Version 1.9.10.0 and HRA/SPECTRALIS® Viewing Module Version 6.0.9.0, Heidelberg Engineering GmbH, Heidelberg, Germany). Follow-up 30-frame SD-OCT scans were performed with Autorescan™ software. CSMT, parafoveal and perifoveal thickness, and TMV values obtained at 28 days and 3 months were compared to those prior to cataract surgery and initiation of anti-inflammatory medi cation.

Macular thickening was defined as CSMT $\geq$ 10% from the baseline with no signs of macular oedema at any postoperative time-point. The diagnosis of PCME was confirmed together with two physicians based on clinical appearance and OCT findings. No pre-existing macular oedema on the preoperative OCT was accepted. The criteria for PCME were CSMT $\geq$ 10% from baseline with cystoid changes near the fovea at any postoperative time-point.

Sample size

The primary outcome measure was changed in CSMT. The sample size estimation was based on the study hypothesis that the preoperative anti-inflammatory treatment group is superior to the postoperative only treatment group in preventing CSMT change 28 days after cataract surgery. CSMT was expected to change +16 μm in the postoperative only treatment group, with a standard deviation of 8 μm. The effect size was set at 5 μm; thus, the CSMT was expected to change +11 μm in the preoperative treatment group, with a standard deviation of 8 μm. With sampling ratio of 1:1, the sample size needed to be at least 41 in each group to provide a test power of 80%. The significance level was set at 5%. With 20% estimated dropout rate, the final estimate was 52 in each group.

Statistical analyses

Data are given as mean $\pm$ standard deviation, except for the absolute numbers and proportions for the nominal scale. IBM SPSS Statistics 24 (IBM Corp., Armonk, NY) was used for statistical analysis. For two-group comparisons at a given time-point, data were analysed with the two-factor chi-squared test for categorical variables, with Student's *t*-test for continuous variables and with Mann–Whitney *U*-test for nonparametric variables. $p \leq 0.05$ was considered statistically significant.

Results

Baseline variables

Baseline variables regarding (i) the patient (age, gender, HbA1c level and insulin dependence), (ii) ophthalmic characteristics (the degree of DR, aqueous flare, CDVA, CSMT and IOP) and (iii) systemic medication were comparable between the two study groups. Baseline characteristics are summarized in Table 2.

Table 2. Baseline variables.

	PRE−	PRE+	p
Age (years)	74.9 ± 8.3	76.6 ± 6.4	0.246
Gender M:F (*n*/%)	27:25 (52:48)	26:25 (51:49)	0.924
HbA1c (mmol/mol)(%)	53.6 ± 14.8 (7.1 ± 1.4)	52.9 ± 16.2 (7.0 ± 1.5)	0.870
Insulin dependence (*n*/%)	21 (40)	23 (45)	0.629
Retinopathy (No:BG:NPDR:PDR) (*n*/%)	37:9:3:3 (71:17:6:6)	39:8:1:3 (76:16:2:6)	0.529
Aqueous flare (pu/ms)	13.5 ± 10.5	16.1 ± 13.7	0.292
CDVA (decimals)	0.35 ± 0.20 (0.05–1.0)	0.37 ± 0.19 (0.05–1.0)	0.561
CSMT (μm)	278.3 ± 32.6 (227–360)	284.7 ± 29.5 (232–363)	0.328
IOP (mmHg)	14.6 ± 3.8 (8–24)	13.2 ± 3.7 (7–22)	0.086
Systemic medication			
ACE/AT2 (*n*/%)	25 (48)	32 (63)	0.134
β-blocker (*n*/%)	25 (48)	28 (55)	0.488
CCB (*n*/%)	14 (27)	16 (31)	0.619
Statin (*n*/%)	32 (62)	29 (57)	0.629

ACE = angiotensin-converting-enzyme inhibitor, AT2 = angiotensin II receptor antagonist, β-blocker = beta-blocker, BG = background retinopathy, CCB = calcium channel blocker, CDVA = corrected distance visual acuity, CSMT = central subfield macular thickness, DM = diabetes mellitus, HbA1c = glycated haemoglobin, IOP = intraocular pressure, NPRD = moderate and severe nonproliferative diabetic retinopathy, PDR = proliferative diabetic retinopathy, pu = photon units, statin = HMG-CoA reductase inhibitor.
Baseline variables regarding patient and ophthalmic parameters. Data are given as mean (±SD) and range (CDVA, CSMT and IOP) or absolute numbers and proportion. For two-group comparisons, two-factor chi-squared test was used for qualitative data, Student's *t*-test for continuous variables and Mann–Whitney *U*-test for ordinal measurement scale in the level of retinopathy and CDVA.

Table 3. Home questionnaire outcomes.

	PRE−	PRE+	p
Duration of conjunctival injection (days)	2.4 ± 1.7	1.6 ± 1.6	0.067
Duration of irritation of the eye (days)	3.3 ± 3.9	2.4 ± 4.0	0.431
Time to reach maximal and stable VA (days)	4.5 ± 3.4	5.0 ± 4.8	0.455
Satisfaction at 28 days (grade 1–10)	9.2 ± 0.8	9.5 ± 0.8	0.166

VA = visual acuity.
Data are given as mean (±SD). For two-group comparisons, Student's *t*-test was used for continuous variables and Mann–Whitney *U*-test for ordinal measurement scale in patient satisfaction grade.

Subjective irritation symptoms and patient satisfaction

Response rate to the structured home questionnaire for patients controlled at 28 days was 65% (33 of 51 patients) in the PRE− group and 67% (32 of 48 patients) in the PRE+ group.

Duration of conjunctival injection after surgery was statistically non-significant between the PRE− (2.4 ± 1.7 days) and PRE+ (1.6 ± 1.6 days) groups (p = 0.067, Table 3). Irritation of the eye after surgery lasted comparably between the groups: 3.3 ± 3.9 days and 2.4 ± 4.0 days, respectively (p = 0.431, Table 3).

Moreover, the time to reach maximal and stable visual acuity (VA) (4.5 ± 3.4 days versus 5.0 ± 4.8 days; p = 0.455, Table 3) and overall patient satisfaction at 28 days on a scale of 0–10 (9.2 ± 0.8 versus 9.5 ± 0.8; p = 0.166, Table 3) did not differ between the PRE− and PRE+ groups.

Aqueous flare, macular thickness and presence of pseudophakic cystoid macular oedema

Aqueous flare change at 28 days was +4.7 ± 12.3 pu/msec in the eyes in the PRE-, compared with −1.9 ± 13.0 pu/msec in the PRE+ group (p = 0.016, Table 4). At 3 months, change in the aqueous flare was +2.6 ± 12.4 pu/msec in the PRE− and −0.2 ± 14.8 pu/msec in the PRE+ group (p = 0.356, Table 4).

CSMT change at 28 days was +2.2 ± 20.2 μm in the PRE- and +0.1 ± 25.2 μm in the PRE+ group (p = 0.670, Table 4). At 3 months, CSMT change was −1.5 ± 26.9 μm and −3.4 ± 26.2 μm, respectively (p = 0.762, Table 4).

Changes from the baseline for parafoveal and perifoveal thickness, and total macular volume at 28 days and at 3 months did not differ between the PRE− and PRE+ groups (Table S1). Furthermore, differences in CDVA gain and IOP reduction at 28 days and at 3 months were insignificant between the study groups (p = NS, Table 4).

At 28 days, macular thickening (CSMT ≥ 10% for baseline with no signs of cystoid changes) was observed in four eyes in the PRE− and two eyes in the PRE+ groups. Importantly, at 3 months macular thickening was not observed in any of the six eyes. During the 3-month follow-up, no cases of PCME were diagnosed in either study group (Table 4).

Self-monitored blood glucose levels during the 28-day follow-up after cataract surgery were comparable between the study groups (6.8 ± 1.6 mmol/l in the PRE- and 7.1 ± 1.9 mmol/l in the PRE+ group; p = 0.670, Table S2). Postoperative self-monitored blood glucose levels did not correlate with aqueous flare or CSMT change (p = NS, data not shown).

Effect of the degree of diabetic retinopathy on cataract surgery outcome measures

Finally, we analysed the outcome measures in eyes with (N = 6) and without

Table 4. Clinical parameter outcomes.

	PRE−	PRE+	p
Aqueous flare (pu/msec)			
Change at 28 days	+4.7 ± 12.3	−1.9 ± 13.0	**0.016**
Change at 3 months	+2.6 ± 12.4	−0.2 ± 14.8	0.356
CDVA (decimals)			
Change at 28 days	+0.44 ± 0.31	+0.46 ± 0.31	0.843
Change at 3 months	+0.46 ± 0.29	+0.53 ± 0.30	0.410
CSMT (μm)			
Change at 28 days	+2.2 ± 20.2	+0.1 ± 25.2	0.670
Change at 3 months	−1.5 ± 26.9	−3.4 ± 26.2	0.762
IOP (mmHg)			
Change at 28 days	−3.1 ± 3.9	−1.7 ± 2.5	0.050
Change at 3 months	−3.5 ± 4.0	−3.1 ± 3.1	0.676
PCME (*N*)			
At 28 days	–	–	
At 3 months	–	–	

CDVA = corrected distance visual acuity, CSMT = central subfield macular thickness, IOP = intraocular pressure, PCME = pseudophakic cystoid macular oedema, pu = photon units.
Data are given as mean (±SD). For two-group comparisons at a given time-point, continuous variables were analysed with the Student's *t*-test and ordinal measurement scale (CDVA) with the Mann–Whitney *U*-test. *p*-value ≤ 0.05 in bold were considered significant.

Table 5. Recovery from cataract surgery in eyes with or without PDR.

	PDR− *N* = 97	PDR+ *N* = 6	p
CDVA (decimals)			
Change at 28 days	+0.47 ± 0.31	+0.24 ± 0.13	0.210
Change at 3 months	+0.52 ± 0.29	+0.33 ± 0.28	0.285
CSMT (μm)			
Change at 28 days	+1.1 ± 23.1	+4.2 ± 7.5	0.745
Change at 3 months	−2.5 ± 27.2	−0.8 ± 16.7	0.831

CDVA = corrected distance visual acuity, CSMT = central subfield macular thickness, PDR = proliferative diabetic retinopathy.
Data are given as mean (±SD). For two-group comparisons at a given time-point, continuous variables (CSMT) were analysed with the Student's *t*-test and ordinal measurement scale (CDVA) with the Mann–Whitney *U*-test.

(*N* = 97) the proliferative form of DR (PDR). Baseline HbA1c levels were 68.5 ± 16.9 mmol/mol (8.4 ± 1.5%) in patients with PDR and 52.2 ± 14.8 mmol/mol (6.9 ± 1.4%) in patients without PDR (p = 0.014, data not shown).

At 28 days, CDVA gain and CSMT change was 0.24 ± 0.13 decimals and +4.2 ± 7.5 μm in patients with PDR, compared to 0.47 ± 0.31 decimals (p = 0.210, Table 5) and +1.1 ± 23.1 μm (p = 0.745, Table 5) in patients without PDR. At 3 months, CDVA gain and CSMT change was 0.33 ± 0.28 decimals and −0.8 ± 16.7 μm in patients with PDR compared to 0.52 ± 0.29 decimals (p = 0.285, Table 5) and −2.5 ± 27.2 μm (p = 0.831, Table 5) in patients without PDR.

CDVA gain and CSMT change at 28 days and 3 months was comparable between the PRE− and PRE+ groups in a subgroup of patients with PDR (p = NS, data not shown) and in another subgroup of patients without PDR (p = NS, data not shown).

Discussion

The results of this study show that the postoperative anti-inflammatory treatment protocol with a combination of potent steroid and NSAID was less effective in controlling ocular inflammation at 28 days, but equally effective in recovery after surgery as the anti-inflammatory protocol containing preoperative treatment for 3 days prior the cataract surgery. Macular oedema was observed in neither of the study groups at 28 days and at 3 months.

The incidence of PCME according to large registry-based studies was higher among diabetic patients compared to those without diabetes. Especially, the prevalence of PCME well correlated with the stage of DR (Chu et al. 2016). Unfortunately, these analyses have been conducted in patients with steroid monotherapy, excluding patients receiving any prophylactic NSAID therapy for PCME. Furthermore, concerns of overestimating diabetes as a risk factor for PCME have been raised due to, for example, the biased postoperative screening between nondiabetic and diabetic patients and the lack of pre-existing information on their macular status (Kim & Grzybowski 2017). Extensive multicentre RCT in nondiabetic patients revealed that combination treatment with bromfenac and dexamethasone reduced the risk for clinically significant macular oedema when compared to patients treated with either drug alone (Wielders et al. 2018a). Treating high-risk patients for PCME with topical NSAIDs may decrease the incidence of macular oedema (Henderson et al. 2007). Randomized clinical trials have previously demonstrated that anti-inflammatory treatment with a combination of NSAID and steroid is more effective than steroid monotherapy in prevention of macular oedema in patients with diabetic retinopathy (Singh et al. 2012; Pollack et al. 2017).

Preoperative use of NSAIDs may have potential to limit pain and miosis during cataract surgery (Hoffman et al. 2016). Donnenfeld et al. have reported that preoperative ketorolac treatment started one to three days before cataract surgery and combined with postoperative combination treatment with prednisolone acetate significantly reduced anterior chamber inflammatory scores and improved visual acuity in the immediate postoperative period when compared to the group of patients on preoperative ketorolac treatment started one hour before cataract surgery with postoperative combination treatment and compared with postoperative steroid only treatment group (Donnenfeld et al. 2006). In their study, no significant effect on

the incidence of cystoid macular oedema was observed (Donnenfeld et al. 2006). In another study, Yavas et al. found that preoperative treatment with indomethacin for 3 days before surgery combined with postoperative combination treatment with prednisolone acetate resulted in significantly lower incidence of angiographic cystoid macular oedema, when compared to the postoperative combination treatment or steroid monotherapy groups (Yavas et al. 2007). In both studies, the postoperative only combination treatment represented relatively high CME incidences. In the study of Yavas et al., the incidence of CME at three months was 15% as evidenced by angiography (Yavas et al. 2007), whereas in the study of Donnenfeld et al., the incidence of CME at 2 weeks was 12% as evidenced by OCT performed to patients with a BCVA worse than 20/30 (Donnenfeld et al. 2006). Furthermore, in both studies diabetes mellitus was an exclusion criterion. In the study of Yavas et al., exclusion criteria were also hypertension, cardiac disease and topical or systemic drug use (Yavas et al. 2007). Comparison of treatment outcomes to those in our study is also hindered by the lack of pre- and postoperative data on macular thickness and aqueous flare in previous studies.

Regardless of progress in topical anti-inflammatory therapy, optimal prevention of PCME accounting cost-effectiveness of the treatment protocol needs further investigation (Kessel et al. 2017). We have recently found that systemic medications may have a bearing on the incidence of PCME (Danni et al. 2018a). When diabetes was appropriately managed, eyes without posterior segment manifestations were not at increased risk for PCME (Danni et al. 2018b), and no excess risk of death, myocardial infarction or stroke was observed, as compared with the general population (Rawshani et al. 2018). Information on cardiovascular medicines and glycemic control are particularly important when defining a prophylactic treatment protocol for PCME of the patients with diabetes. As a NSAID regimen, we chose to use nepafenac, which is one of the most commonly used NSAIDs, and has proven to be effective and well tolerated (Margulis et al. 2017; Ylinen et al. 2018). We analysed not only the preoperative glycemic control, but also the postoperative glucose levels, as cataract surgery may positively affect glycemic control (Bar-Oz et al. 2018). Not only the posterior segment status of diabetic patients, but also the glycemic control pre- and postoperatively and systemic medication were comparable between the study groups. Of note, even the presence of the proliferative form of diabetic retinopathy was not associated with the development of macular oedema with the anti-inflammatory combination treatment in our study.

For the PCME analysis, the patient number in this study is relatively small, and the follow-up of 3 months is short. The incidence of clinically significant CME after uneventful cataract surgery is low even in the diabetic population (from 3% to 4%) (Schmier et al. 2007; Chu et al. 2016; Wielders et al. 2018b). Late occurrence of clinically significant CME may develop, beyond the 3-month follow-up period particularly among patients with diabetic posterior segment manifestations (Baker et al. 2013; Denniston et al. 2017). Thus, larger patient series are necessary to reach more reliable results, and in this study, the effectiveness of anti-inflammatory combination treatment to counteract PCME may have been overestimated. Furthermore, it should be noted that no patients had prior or active DME in this study as prior or scheduled anti-VEGF treatment was one of the exclusion criteria.

Adding a NSAID to prednisolone acetate treatment was associated with reduced risk of macular oedema (Shorstein et al. 2015). Generally, however, in diabetic patients fixed or tapering-down schedule with topical NSAID is longer than the 3 weeks adopted in this study. As previously described, aqueous flare peaks within the first few days after cataract surgery, after which the levels decline rapidly in the first week and return to baseline by 3 months (Stock et al. 2011). High aqueous flare levels by contrast were associated with multiple pro-inflammatory and vasoactive cytokines, and PCME development (Ersoy et al. 2013; Noma et al. 2017). Aqueous flare remained slightly elevated in the postoperative only treatment group at 3 months and it may be important for clinical practice regarding late occurrence of macular oedema. The longer anti-inflammatory treatment may be especially important in eyes with prior history of or manifest DME.

In conclusion, our results emphasize that diabetic patients without DME do not require preoperative treatment protocol against PCME when the postoperative anti-inflammatory treatment is adequate.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Table S1. Macular thickness and volume.

Table S2. Self-monitored fasting and postprandial blood glucose levels during the 28-day follow-up after cataract surgery.